already present in claim 15.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

Remarks

I. Addressing the Examiner's Rejections.

1. Rejection of Claims 7, 25, and 34 under 35 U.S.C. §112, Second Paragraph.

The Examiner rejected claims 7, 25, and 34 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner asserted that there is insufficient antecedent basis for the limitation "the time interval n+1."

Claims 7, 25, and 34 are amended herein. Applicants submit that the amendments to the claims (i.e., removal of "the" and addition of "wherein") overcome the rejection of the claims.

In view of the amendments to claims 7, 25, and 34, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

2. Rejection of the Claims Under 35 U.S.C. §103(a).

The Examiner has rejected claims 1-34 under 35 U.S.C. §103(a) asserting that the claims are obvious over Kurnik (WO 99/58973) in view of Tamada, et al. (JAMA 282(19):1839-1844, 17 November 1999).

For the reasons of record (i.e., set forth in applicants' response dated 3 December 2003), the applicants maintain that the USPTO has failed to establish a *prima facie* case of obviousness.

In the final Office action, the Examiner asserts the following:

> Applicant's arguments filed 12/8/03 have been fully considered but they are not persuasive. In response to the argument that KURNIK neither teaches nor suggests prediction of hypoglycemia by comparing both a predicted measurement value and a parameter value (current) or trend of parameter values to a threshold, it is noted that KURNIK teaches measurement of glucose in "real time" and prediction of future levels of glucose (pages 42 and 44), and teaches that these measurements may be used to predict hypoglycemic episodes (p. 51). Claim 1 of KURNIK (p. 54) specifically recites BOTH determination of an analyte concentration at the time of extraction, and prediction of a measurement value at a future time. (Final

Office action, page 3, lines 1-9.)

The Examiner has mischaracterized applicants' previously presented arguments. Applicants previously argued the following:

> The Kurnik reference neither teaches nor suggests a multiple step approach to predicting a hypoglycemic event in a subject when **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject. (Emphasis in original.)

The Examiner has focused on measurement of glucose values in real-time and predicted glucose measurement values but has completely failed to provide any teaching in Kurnik related to "(ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject." The Examiner improperly conflates the trend of parameter values **(defined in the claims as either skin conductance or temperature of the subject)** with a trend of glucose values. There is no teaching in Kurnik (or Tamada) to **measure skin conductance or temperature as measurements to be used in addition to a predicted glucose value at a further time interval to improve a prediction of a hypoglycemic event**. The Kurnik reference teaches the use of skin conductance and temperature values only in the context of enabling "temperature correction of sensor signals" and "data screening correction or invalidation of sensor signals" (see, for example, the Kurnik reference, page 32, line 28, to page 33, line 5). In one particular aspect of the Kurnik reference, a raw signal is obtained using a transdermal sampling system that is placed in operative contact with a skin or mucosal surface of a biological system (e.g., the Kurnik reference, page 3, lines 22-25). It is only in the context of a monitoring system comprising an exemplary transdermal sampling device (i.e., an iontophoretic glucose sampling device) that skin conductance and temperature are discussed in the Kurnik reference.). These teachings relate only to variables, such as sweat and temperature, that might affect the functioning of the iontophoretic glucose sampling device and its ability to

provide accurate glucose readings. For example, noting that perspiration contains glucose (Kurnik, page 43, line 7), the Kurnik reference stated the following in context:

> For example, perspiration contains glucose, and perspiration occurring rapidly and in sufficient quantities **may affect the detected signal either before or during biosensor measurement.** (Emphasis added, the Kurnik reference, page 43, lines 7-10.)

This interpretation of the reference is confirmed by the following teaching in the Kurnik reference:

> The housing **32** can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs **to enable temperature correction of sensor signals**. The housing can also include an optional conductance sensing element (e.g., an integrated pair of electrodes) which monitors the conductance at the skin or mucosal surface **to enable data screening correction or invalidation of sensor signals** (Emphasis added, the Kurnik reference, page 32, line 28, to page 33, line 5.)

The Kurnik reference neither teaches nor suggests a multiple step approach to predicting a hypoglycemic event in a subject when **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject.

Accordingly, the Examiner has not considered the claims "as a whole" as required for a determination of obviousness:

> The '315 patent specifically stated that it disclosed and claimed a combination of features previously used in two separate devices. That fact alone is not fatal to patentability. The claimed invention must be considered as a whole, and the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Lindermann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481, 488 (Fed. Cir. 1984).

In the present application, independent claims 1, 15, and 26 all include **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a

hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is **skin conductance or temperature** of the subject. As opposed to the Examiner's statement that "Claim 1 of KURNIK (p. 54) specifically recites BOTH determination of an analyte concentration at the time of extraction, and prediction of a measurement value at a future time." At most this teaching of Kurnik, cited by the Examiner, relates to only part (i) "comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval" of each independent claim.

Further, the Examiner asserts the following regarding the teachings of the Tamada reference:

> In response to the argument that TANADA [sic] does not provide the "deficiencies" of KURNIK, does not teach a predicted measurement value, and does not teach measurement using both temperature and skin conductance, applicant is reminded that the rejection made over a combination of references, wherein KURNIK further teaches that both skin conductance (sweat) and temperature may be used to measure glucose (p. 43). As set forth in the previous office action, KURNIK teaches the desirability of predicting hypoglycemia before a "critical level" of glucose is reached (p. 51-52), but des [sic] not specifically teach comparison to a threshold level. TAMADA is relied upon for teaching that hypoglycemia may be diagnosed/predicted when glucose levels fall below a specific threshold level, also as previously set forth. (Final Office action, page 3, lines 9-20.)

In view of the Examiner's argument that the Tamada reference is only being relied on to teach a "threshold level," applicants submit that the Examiner has clearly failed to establish a case of *prima facie* obviousness because the cited references do not even teach all of the elements of the claimed invention (for the reasons of record set forth in applicants' response dated 3 December 2003). Specifically, Kurnik does not teach "comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is skin conductance or temperature of the subject" (claim 1 of the present application) or "comparing said skin conductance readings or temperature readings with a threshold parameter value or trend of parameter values indicates a hypoglycemic event" (claims 15 and 26 of the present application). The Tamada reference contains no teaching concerning the establishment

threshold levels for measurements of skin conductance or temperature as indicators of hypoglycemia in addition to use of a predicted glucose measurement value that indicates a hypoglycemic event at a further time interval.

The Examiner's assertion that "KURNIK further teaches that both skin conductance (sweat) and temperature may be used to measure glucose" is confusing and misleading. A glucose-specific signal at a sensing electrode is used to measure glucose, for example, by providing a raw signal, for example, as follows:

> When the reaction is complete, the process is repeated and a subsequent measurement is obtained. More specifically, the iontophoretic current is again applied, glucose is drawn through the skin surface into the collection reservoir, and the reaction is catalyzed in order to create a biosensor current. These sampling (extraction) and sensing operations are integrated such that glucose from interstitial fluid directly beneath the skin surface is extracted into the hydrogel collection pad where it contacts the GOx enzyme. **The GOx enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to a Pt-based sensor and reacts with the sensor to regenerate oxygen and form electrons. The electrons generate an electrical signal that can be measured, analyzed, and correlated to blood glucose.** (Emphasis added, the Kurnik reference, page 28, line 25, to page 29, line 8.)

The Kurnik reference teaches that such a raw signal can then be converted to an analyte specific value (e.g., a glucose value) using a calibration step, for example as follows:

> The raw signal is then converted into an analyte specific value using a calibration step which correlates the signal obtained from the sensing device with the concentration of the analyte present in the biological system. **A wide variety of calibration techniques can be used to interpret such signals. These calibration techniques apply mathematical, statistical and/or pattern recognition techniques to the problem of signal processing in chemical analyses, for example, using neural networks,** genetic algorithm signal processing, 40 linear regression, multiple-linear regression, or principal components analysis of statistical (test) measurements. (Emphasis added, the Kurnik reference, page 40, line 23, to page 41, line 3.)

The calibration step can be carried out, for example, using a neural network or genetic algorithm, for example, as follows:

> **In one particular embodiment, the calibration step can be carried out using artificial neural networks** or genetic algorithms. The structure of a particular neural network algorithm used in the practice of the invention can vary widely; however, the network should contain an input layer, one or more

hidden layers, and one output layer. Such networks can be trained on a 41 test data set, and then applied to a population. There are an infinite number of suitable network types, transfer functions, training criteria, testing and application methods which will occur to the ordinarily skilled artisan upon reading the instant specification. (Emphasis added, the Kurnik reference, page 41, line 26, to page 42, line 5.)

Inputs into such a calibration algorithm can, for example, include the following:

In the context of the iontophoretic glucose sampling device described hereinabove, a preferred neural network algorithm could use, for example, the following inputs to provide a blood glucose measurement: time; **signal from the active reservoir/signal from the blank reservoir; signal from two active reservoirs (averaged or cumulative);** calibration time; skin temperature; voltage; skin conductivity; and, when operating in the training mode, measured glucose.

For example, perspiration contains glucose, and perspiration occurring rapidly and in sufficient quantities may affect the detected signal either before or during biosensor measurement. Accordingly, a sensor can be used to monitor perspiration levels for a given measurement cycle at time points before, during, and/or after iontophoresis, and before, during, and/or after glucose sensing. Although a number of different mechanisms can be used, skin conductance can be readily measured with a device contacted with the skin. **Skin conductivity is related to perspiration.**

In a similar manner, a sensor can be used to measure skin temperature for a given measurement cycle at time points before, during, and/or after iontophoresis, and before, during, and/or after glucose sensing. (Emphasis added, the Kurnik reference, page 42, line 30, to page 43, line 22.)

These last two paragraphs of the Kurnik reference is the teaching, regarding skin conductance and temperature, being relied upon by the Examiner in the assertion that "KURNIK further teaches that both skin conductance (sweat) and temperature may be used to measure glucose". However, as can be seen when considering this teaching as a whole, skin conductance and temperature in the Kurnik reference do not "measure glucose." Rather, these are variables involved in determination of the reliability of the glucose-related signal obtained from the monitoring device sensor. The Kurnik reference explicitly teaches this role of skin conductance and temperature readings, for example, as follows:

The housing **32** can further include an optional temperature sensing element (e.g., a thermistor, thermometer, or thermocouple device) which monitors the temperature at the collection reservoirs **to enable temperature correction of sensor signals**. The housing can also include an optional

conductance sensing element (e.g., an integrated pair of electrodes) which monitors the conductance at the skin or mucosal surface **to enable data screening correction or invalidation of sensor signals.** (Emphasis added; the Kurnik reference, page 32, line 28, to page 33, line 5).

Accordingly, **measurements of skin conductance and temperature readings as taught by the Kurnik reference are used to qualify sensor measurements, wherein the sensor measurements provide glucose specific signal, not as additional indicators of possible hypoglycemic events** as is required by the limitations of the independent claims of the present application, for example, independent claim 1, as follows (emphasis added):

1. A method for predicting a hypoglycemic event in a subject, said method comprising

determining (i) a threshold glucose value that corresponds to said hypoglycemic event, and (ii) at least one threshold parameter value that is correlated with said hypoglycemic event, wherein at least one threshold parameter value is skin conductance or temperature;

obtaining a series of glucose measurement values at selected time intervals using a method comprising

extracting a sample comprising glucose from the subject using a transdermal sampling system that is in operative contact with a skin or mucosal surface of said subject;

obtaining a raw signal specifically related to a glucose amount or concentration in the subject;

correlating the raw signal with a glucose measurement value indicative of the amount or concentration of glucose present in the subject at the time of extraction;

repeating said obtaining and correlating to provide a series of measurement values at selected time intervals;

predicting a measurement value at a further time interval subsequent to said series of measurement values; and

comparing said predicted measurement value to said threshold glucose value, wherein a measurement value lower than the threshold value is designated to be hypoglycemic;

measuring at least one parameter value or trend of parameter values concurrently, simultaneously, or sequentially with said obtaining of the series of measurement values, wherein the parameter value or trend of parameter values is (i) correlated with said hypoglycemic event, and (ii) reflective of skin conductance readings or temperature readings of the subject, and comparing said parameter value or trend of parameter values with said threshold parameter value to determine whether said parameter value or trend of parameter values indicates a hypoglycemic event; and

predicting a hypoglycemic event in said subject when **both** (i)

> comparing said **predicted measurement value to said threshold glucose value** indicates a hypoglycemic event at said further time interval, **and** (ii) **comparing said parameter value or trend of parameter values with said threshold parameter value indicates a hypoglycemic event**.

The Examiner, in the final Office action, asserts an expectation of success not found in the references, as follows:

> As both KURNIK and TAMADA teach detection of hypoglycemia, the examiner maintains that one of skill in the art would reasonably have expected success in predicting hypoglycemia in the method of KURNIK by comparing both the current and predicted glucose measurement of KURNIK to a defined threshold value, as taught by TAMADA. (Final Office action, page 3, line 20, to page 4, line 2)

Again, the Examiner has mischaracterized applicants' invention. The method of the present invention requires **both** (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at a further time interval, **and** (ii) comparing a parameter value or trend of parameter values with a threshold parameter value indicates a hypoglycemic event, wherein at least one of the parameters is **skin conductance or temperature** of the subject.

The method of the invention does not simply use of "current and predicted glucose measurements of KURNIK to a defined threshold value, as taught by TAMADA" as asserted by the Examiner. The Examiner has provided no teaching of, for example, determining a hypoglycemia-related threshold value for skin conductance (see claim 1, "**determining** (i) a threshold glucose value that corresponds to said hypoglycemic event, and (ii) **at least one threshold parameter value that is correlated with said hypoglycemic event**, wherein at least one threshold parameter value is **skin conductance** or temperature," emphasis added), measuring skin conductance (see claim 1, "**measuring** at least one parameter value or trend of parameter values concurrently, simultaneously, or sequentially with said obtaining of the series of measurement values, wherein the parameter value or trend of parameter values is (i) correlated with said hypoglycemic event, and (ii) reflective of **skin conductance** readings or temperature readings of the subject," emphasis added), comparing the measured skin conductance value to the hypoglycemia-related threshold value for skin conductance (see claim 1, "**comparing said parameter value** or trend of parameter values **with said**

threshold parameter value to determine whether said parameter value or trend of parameter values **indicates a hypoglycemic event,**" emphasis added), and predicting a hypoglycemic event in a subject when both (i) comparing a predicted measurement value to a threshold glucose value indicates a hypoglycemic event at said further time interval, and (ii) comparing the measured skin conductance value with a hypoglycemia-related threshold value for skin conductance indicates a hypoglycemic event (see claim 1, "predicting a hypoglycemic event in said subject when **both** (i) comparing said predicted measurement value to said threshold glucose value indicates a hypoglycemic event at said further time interval, **and** (ii) **comparing said parameter value** or trend of parameter values **with said threshold parameter value indicates a hypoglycemic event,**" emphasis added).

The Examiner asserts that the motivation to combine the references "would have been to include parameters known to be associated with hypoglycemia, as taught by both KURNIK and TAMADA" (final Office action, page 4, lines 6-7).

First, as pointed out above not all the elements of the invention are taught by the combination of the references set forth by the Examiner.

Second, the mere presence of elements of a claimed invention in multiple references does not provide the requisite motivation. As noted above,

> The claimed invention must be considered as a whole, and the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Lindermann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481, 488 (Fed. Cir. 1984).

Further, in *Bausch & Lomb v. Barnes-Hind/Hydrocurve* (796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986)), the U.S. Court of Appeals for the Federal Circuit emphasized the following:

> It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

There must be some teaching or suggestion in the cited references of the desirability of the modifications suggested by the Examiner:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion

> supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (quoting *ACS Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). . . . The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780, 1783–84 (Fed. Cir. 1992).

If the reference of Kurnik is, as suggested by the Examiner, sufficient to predict hypoglycemic events, there is no motivation nor desirability to modifying the teachings of the Kurnik reference as proposed by the Examiner. Again, the Examiner has not even provided a teaching of trend analysis of skin conductivity or temperature specifically related to a hypoglycemia-associated threshold to modify the teaching of Kurnik, let alone the desirability of making such a modification.

Third, the motivation has only been provided by the Examiner using hindsight reconstruction. Such hindsight reconstruction is prohibited. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Regarding hindsight reasoning the Examiner asserts the following:

> In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The Examiner's reliance on *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971) is misplaced. *McLaughlin* in no way held that common knowledge is a substitute for evidence. Nor does *McLaughlin*, decided in 1971, outweigh the many Federal Circuit and

CCPA decisions that the prior art **as a whole** must suggest the desirability of the making the claimed combination. Virtually all inventions are combinations of old elements. *See, e.g., In re Rouffet,* 149 F.3d 1350, 47 USPQ 2d 1453, 1457 (Fed. Cir. 1998). Thus, the requirement is not whether each claimed element can be identified individually in a reference but rather whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet,* 149 F.3d 1350, 47 USPQ 2d 1453, 1458 (Fed. Cir. 1998). In the present case, the Examiner has not shown, with evidence, such reasons and, accordingly, has not established a *prima facie* case of obviousness.

In view of the arguments presented above, applicants submit that the Examiner has failed to establish a case of *prima facie* obviousness. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §103 be withdrawn.

Conclusion

Applicants submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 599-3591.

Respectfully submitted,

Date: 17 May 2004

By: Gary R Fabian

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